GYNECOLOGY

Familiality analysis of provoked vestibulodynia treated by vestibulectomy supports genetic predisposition

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BACKGROUND: Provoked vestibulodynia is a poorly understood disease that affects 8—15% of women in their lifetime. There is significant inflammation and nerve growth in vestibular biopsies from affected women treated by vestibulectomy compared with matched female population controls without vestibulodynia. The triggers leading to this neurogenic inflammation are unknown, but they are likely multifactorial.

OBJECTIVE: Our objective was to determine whether vestibulodynia is more common in close and distantly related female relatives of women diagnosed with the disease and those specifically treated by vestibulectomy. Excess familial clustering would support a potential genetic predisposition for vestibulodynia and warrant further studies to isolate risk alleles.

STUDY DESIGN: Using population-based genealogy linked to University of Utah Hospital CPT coded data, we estimated the relative risk of vestibulectomy in female relatives of affected women. We also compared the average pairwise relatedness of cases to the expected relatedness of the population and identified high-disease-burden pedigrees.

RESULTS: A total of 183 potential vestibulectomy probands were identified using CPT codes. The relative risk of vestibulectomy was elevated in first-degree (20 [6.6—47], $P < .00001$), second-degree (4.5 [0.5—16], $P = .07$), and third-degree female relatives (3.4 [1.2—8.8], $P = .03$). Seventy of these 183 CPT-based probands had available clinical history to confirm a diagnosis of moderate to severe vestibulodynia. Notably, this smaller group of confirmed probands (n = 70) revealed a similar familiality in first-degree (54 [17.5—126], $P < .00001$), second-degree (19.7 [2.4—71], $P = .005$), and third-degree relatives (12 [3.3—31], $P = .0004$), despite less statistical power for analysis. Overall, the average pairwise relatedness of affected women was significantly higher than expected ($P < .001$) and a number of high-disease-burden Utah families were identified.

CONCLUSION: Our data suggest that vestibulodynia treated by vestibulectomy has a genetic predisposition. Future studies will identify candidate genes by linkage analysis in affected families and sequencing of distantly related probands.

Key words: vestibulodynia, vestibulectomy, familiality, genetics, Utah Population Database

Provoked vestibulodynia (PVD) occurs in approximately 8—15% of women during their lifetime and is the leading cause of dyspareunia (painful intercourse).[1-4] It is characterized by severe localized pain in the vestibule in response to pressure applied by cotton swab.[2,5] The impact of this common disease is reduced quality of life, higher rates of sexual dysfunction, and significant psychological distress.[6-10]

A variety of noninvasive treatments have been tried, but they lack a rational understanding of the underlying cause and are often ineffective.[4,6] It is clear that a better understanding of PVD is needed to provide clinicians with more objective diagnostic tests and more rational therapeutic targets. We and others[11-20] have shown that vestibulectomy tissue specimens have increased chronic inflammation, mast cell recruitment, and conspicuous submucosal nerve growth compared with vestibular biopsies from unaffected women. There are also more CD4-positive T cells, which may provide insights into the triggers of this neurogenic inflammation;[21] in some cases, a plasma cell—mediated process may be involved.[22] Unfortunately, therapies aimed at treating the chronic inflammation, or providing neuromodulation, are often ineffective.[4,23-25]

EDITORS' CHOICE

Our prior studies have largely been based on women with chronic disease recalcitrant to alternative therapies, prompting vestibulectomy for relief.[4,18-21] The problem is that PVD is usually diagnosed after years of symptoms and the tissue is already remodeled.[19,20] New predictive markers are needed to identify women at risk for PVD and provide early interventions to prevent the chronic neurogenic inflammation and tissue remodeling in these select patients.

We hypothesize that PVD may have a genetic predisposition. Many chronic diseases have a genetic predisposition with risk alleles that may serve as both diagnostic aides and insights into pathogenic mechanisms. PVD is not currently considered a genetic disease, but there are reports of a potential association with seasonal allergies,[26] proinflammatory cytokines (eg, mannose-binding lectin, IL-6, IL-1β[27-30]), and aberrant hormone regulation.[31] Genetic testing in women with PVD is only in the early stages of discovery, but other potential candidate genes may include common mediators of neurogenic inflammation.[32-34]

Population-based analysis of the familial clustering of a disorder is an informative approach to test for evidence of a genetic contribution to common chronic diseases like PVD.[35,36] Once evidence for a genetic contribution to

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disease risk is determined, studies of affected individuals in high-risk pedigrees can identify risk alleles.[36] For example, a number of familial studies have determined that interstitial cystitis,[37-39] which is commonly associated with PVD,[40] has a genetic predisposition. This is important, because both diseases present with pain and neurogenic inflammation.[41] Perhaps these 2 common diseases share genetic risk factors and pathogenic triggers? Indeed, risk allele studies of interstitial cystitis have revealed promising candidate genes like IL-4 and IL-10 variants[34,42] involved in T-cell regulation that we suspect may also play a role in PVD.[21]

To test whether there is a significant heritable contribution to PVD, we employed the Utah Population Database (UPDB), which links genealogy information for millions of individuals to medical diagnostic data (ICD-9 and CPT codes). This approach has been validated and revealed genetic contributions to a number of common diseases.[35,36,43]

Materials and Methods

The Utah Population Database

The UPDB (www.healthcare.utah.edu/huntsmancancerinstitute/research/updb/) computerized genealogic data for the Utah pioneers and their descendants (from the mid-1800s) has been linked to diagnoses and procedural outcomes from the University of Utah Health Sciences Center (UUHSC) for patients treated from 1994 to present. The genealogy includes over 8 million unique individual records; 1.3 million of these individuals have at least 3 generations of genealogy data available meeting inclusion criteria. Inclusion criteria for familial clustering analyses required all subjects (cases and matched population controls) to have genealogy information available for at least 12 of 14 of their immediate ancestors (ie, parents, all grandparents, and at least 6 of 8 great-grandparents). These inclusion criteria have been determined to provide sufficient sensitivity to reasonably detect affected first-, second-, and third-degree relatives.[35,36,43] All analyses used coded data (nonidentifiable).

Identification of PVD subjects

The study was approved by the Oregon Health & Science University (IRB #011064) and the University of Utah (IRB #068774 and #53474) Institutional Review Boards. It was also approved by the Utah Resource for Genetic and Epidemiological Research, which oversees the UPDB. We used 2 approaches to identify cohorts of women with dyspareunia related to vestibulodynia. First, we employed a broad search using all potential CPT codes employed for vestibulectomy: 56620 (n = 150), 56625 (n = 0), 56630 (n = 14), 56631 (n = 3), 56632 (n = 8), 56633 (n = 1), 56634 (n = 3), 56635 (n = 0), 56637 (n = 3), and 56640 (n = 1), for a total of 183 potentially affected vestibulodynia cases diagnosed at the University of Utah and treated by vestibulectomy. Second, we had a cohort of 216 cases of vestibulodynia treated by vestibulectomy by 1 surgeon (H.S.) for cross-referencing with the UPDB. Seventy (70/216) of these confirmed probands linked to the UPBD had adequate ancestry to be included in a separate analysis. These clinically confirmed vestibulectomy cases were all diagnosed using Friedrich criteria[1] and they had no other identifiable reason for dyspareunia (eg, vulvar dermatosis, infectious vaginitis).[2] All of these confirmed cases had reported severe or moderate dyspareunia for at least 6 months; they were all refractory to conservative management (eg, topical anesthetics, corticosteroids, physical therapy, and neuromodulators); and they all had vestibulectomies.[44]

Population controls and CPT code–based vestibulectomy rates

Female population controls were randomly selected from UUHSC patients that were matched to cases based on sex, birthplace (urban/rural based on Utah birth county residence), and birth year (5-year birth cohorts), similar to our other previous publications.[35,45] Population-based rates of vestibulectomy were estimated by using all UUHSC data linked to the UPDB. All 1.3 million UPDB individuals with at least 12 of their 14 immediate ancestors were assigned to 1 of 205 cohort "bins" based on cohort characteristics. UUHSC population cohort-specific rates of vestibulectomy were estimated by dividing the number of vestibulectomy cases identified by CPT code at UUHSC in each cohort by the total number of UUHSC female subjects in the cohort.

Relative risk

We estimated the relative risk of vestibulectomy among relatives of cases as the ratio of the number of observed cases to the number of expected cases in the population. The observed number of affected relatives of probands treated at UUHSC with CPT code-based vestibulectomy was counted among the specific degree of relatives of interest (eg, first-degree). The expected number of cases was calculated by multiplying the number of relatives of interest in each cohort (eg, first-degree) who were patients at UUHSC times the estimated rate of vestibulectomy for each cohort, and then summing across all of the cohorts as described.[35,43] The relative risk is assumed to follow a Poisson distribution, with the mean value equal to the expected number of cases (ie, null hypothesis has a relative risk = 1.0). Significance was determined by Fisher exact test.

Genealogical Index of Familiality statistic

The Genealogical Index of Familiality (GIF) statistic uses the Malécot coefficient of kinship to measure the probability that a pair of individuals share an identical copy of a chromosome region by descent from a common ancestor in the UPDB.[35] GIF analysis tests the hypothesis that affected cases may be more related to each other than expected compared with the relatedness of matched sets of similar women in the population. In turn, we compared the average pairwise relatedness of CPT code-based vestibulectomy cases with the mean average pairwise relatedness of 1000 sets of randomly selected but age- and region-matched female controls. The distribution of the GIF statistic for the 1000 sets of population controls represented the expected pairwise relatedness of these women in the Utah population. The GIF statistic for the